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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,843	11/25/2003	Robert J. Ternansky	34433/US/4/AMP/SKS	8174

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Jones Day
222 East 41st Street
New York, NY 10017

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,843	TERNANSKY ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-70 and 75* is/are pending in the application.

4a) Of the above claim(s) *68-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-67 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on March 1, 2007.

Claims 64-70 and new claim 75 are pending in the application.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Upon reconsideration, the species elected by Applicant (Ac-PHSC(Ac)N-doxorubicin), previously deemed free of the prior art (Office Action of November 1, 2006) has now been rejected over a 103 obviousness rejection set forth below. In addition, the species Ac-PHSCN-doxorubicin, found during the update of the search, has also been examined. Claims 68-70 are withdrawn as not drawn to either examined species.

Claims 64-67 and 70 are presented for examination on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livant (US 6,001,965, citation A19 in the IDS of August 11, 2006) in view of Livant et al. (Cancer Research, 2000, cited in the PTO-892 of August 11, 2005) and in view of DeFeo-Jones et al. (Nature Medicine, 2000).

Livant teaches PHSCN which has chemotherapeutic activity thus inhibiting the growth or metastasis of tumors (column 5, lines 36-44 and 51-55, Examples 9 and 11). Livant uses PHSCN to inhibit growth and metastasis of prostate cancer at Examples 12-13. Livant teaches that PHSCN can be administered alone or in combination with antiproliferative drugs in a neoadjuvant setting to reduce the metastatic load in the patient (column 15, lines 40-50). Livant also teaches chemical hybrids of PHSCN covalently linked to a targeting carrier or to an active pharmaceutical (column 16, lines 1-9). Livant also teaches blocking the amino terminus by acetylation and the carboxyl terminus by amidation (e.g., Ac-PHSCN-NH_2) to prevent digestion by exopeptidases. See also Livant et al. (Cancer Research, 2000) teaching that Ac-PHSCN-NH_2 is 30 times more potent than PHSCN (e.g., abstract, Figures 6-9). The limitations of claims 64-66 are taught, e.g., at Ac-Pro-His-Ser-Cys-Asn-NH_2 [Ac-PHSCN-NH_2] wherein s is 0, r is 0, R_{30} is Ac, X_2 is Pro, X_3 is His, X_4 is Ser, X_5 is Cys [y is 0, n is 1 and R_{13} is H], X_6 is

Asn [m is 1], R_4 is H (e.g., abstract, lines 6-7 and 21-22 of Cancer Research and see, e.g., claims 1-3 of US '965) and R_{31} is a targeting carrier or an active pharmaceutical (e.g., column 16, lines 1-9 of US '965).

Livant does not teach conjugation of Ac-PHSCN-NH_2 to a targeting carrier comprising doxorubicin (i.e., R_{31} being a targeting agent comprising doxorubicin).

DeFeo-Jones et al. teach L-377,202, a conjugate of doxorubicin and a prostate specific antigen (PSA) hydrolyzable peptide (e.g. page 1251, column 1, lines 5-19). Drug locatization studies demostrated that L-377,202 is a targeting carrier to PSA secreting tissues that selectively kills PSA-secreting tumor cells in culture (page 1248, column 2, lines 15-25 and page 1249, column 1,lines 1-15 and Figure 3, page 1251). Serum PSA levels correlate with the existence and extent of prostate cancer; higher levels indicate a larger tumor burden, including metastatic disease (e.g., page 1248, column 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the conjugates of the more potent Ac-PHSCN-NH_2 with targeting carriers taught by Livant by conjugating to the targeting carrier "doxorubicin-PSA hydrolyzable peptide" taught by DeFeo-Jones et al. One of ordinary skill in the art would have been motivated to do so because Livant teaches Ac-PHSCN-NH_2 inhibits growth and metastasis of prostate cancer (Examples 12-13) and because "doxorubicin -PSA hydrolyzable peptide" is a targeting carrier that selectively targets prostate cancer as taught by DeFeo-Jones et al. (e.g., page 1248, column 2, lines 15-25 and page 1249, column 1,lines 1-15 and Figure 3, page 1251). There would have been reasonable expectation of success because it was known that Ac-PHSCN-NH_2 could be

administered in combination with antiproliferative drugs in a neoadjuvant setting to reduce the metastatic load in the patient such as chemical hybrids covalently linked to targeting carriers e.g. by attaching via the aminated end as taught by Livant. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 64-67 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livant (6,001,965) in view of Livant et al. (Cancer Research, 2000, cited in the PTO-892 of August 11, 2005) and in view of DeFeo-Jones et al. (Nature Medicine, 2000) and in further view of Carpino et al. (US 4,394,519).

Livant, Livant et al. and DeFeo-Jones et al. are relied upon as above.

Livant, Livant et al. and DeFeo-Jones et al. do not teach acetylating the cysteine in Ac-PHSCN-NH2 to make Ac-PHSC(Ac)N-NH_2.

Carpino et al. teach that sulfhydryl groups (such as in cysteines) may cause secondary reactions during peptide synthesis and therefore blocking them would prevent them (e.g., see background of the invention and preparation of blocked amino acids and peptides sections) including acylation reactions.

Carpino et al. do not expressly teach blocking the sulfhydryl with acetyl (Ac).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the peptide Ac-PHSCN-NH_2 by blocking the cysteine. One skilled in the art would have been motivated to do so during the peptide synthesis process in order to avoid secondary reactions of the sulfhydryl group of the cysteine.

There would have been a reasonable expectation of success because peptide synthesis in solution by classic or various repetitive methods or on a solid support (Merrifield) were well known techniques and because acylation reactions were known in the art (e.g., background of the invention). The adjustment of particular conventional working conditions (e.g., i.e., the use of acetyl (acyl group) as blocking agent in the cysteine residue to avoid undesirable secondary reactions within such conjugates) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

MMCG 06/07

6/11/07
ANISH GUPTA
PRIMARY EXAMINER